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Acquisition of Rectal Colonization by Vancomycin-Resistant *Enterococcus* among Intensive Care Unit Patients Treated with Piperacillin-Tazobactam versus Those Receiving Cefepime-Containing Antibiotic Regimens▽

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In contrast to expanded-spectrum cephalosporins, beta-lactam–beta-lactamase inhibitor combinations such as piperacillin-tazobactam have rarely been associated with vancomycin-resistant *Enterococcus* (VRE) colonization and infection. In mice, piperacillin-tazobactam has sufficient antienterococcal activity to inhibit the establishment of colonization during treatment, but this effect has not been confirmed in human patients. We prospectively evaluated the acquisition of rectal colonization by VRE among intensive care unit patients receiving antibiotic regimens containing piperacillin-tazobactam versus those receiving cefepime, an expanded-spectrum cephalosporin with minimal antienterococcal activity. Rectal swabs were obtained weekly and were cultured for VRE. For 146 patients with a negative rectal swab for VRE prior to therapy, there was no significant difference in the frequency of VRE acquisition between patients receiving piperacillin-tazobactam- and cefepime-containing regimens (19/72 [26.4%] and 23/74 [31.1%], respectively; $P = 0.28$). Of the 19 patients who acquired VRE in association with piperacillin-tazobactam, 10 (53%) developed the new detection of VRE during therapy. Patients initiated on treatment with cefepime-containing regimens were significantly more likely than those initiated on treatment with piperacillin-tazobactam-containing regimens to have received antibiotic therapy in the prior 30 days (55/74 [74.3%] and 22/72 [30.6%], respectively; $P < 0.001$). These findings suggest that piperacillin-tazobactam- and cefepime-containing antibiotic regimens may be associated with the frequent acquisition of VRE in real-world intensive care unit settings. Although piperacillin-tazobactam inhibits the establishment of VRE colonization in mice when exposure occurs during treatment, our data suggest that this agent may not prevent the acquisition of VRE in patients.

Antibiotics play a crucial role in the pathogenesis of vancomycin-resistant *Enterococcus* (VRE) intestinal colonization (6, 7). Studies performed with mouse models suggest that the effect of antibiotics on colonization represents a balance between promotion due to the suppression of anaerobes that compete with VRE and inhibition due to antimicrobial activity against VRE strains (7, 16). Antibiotics that do not disrupt the anaerobic microflora (e.g., cefepime and aztreonam) do not promote VRE colonization in mouse models (7). Antibiotics that disrupt the anaerobic microflora and that possess minimal antienterococcal activity (e.g., ceftriaxone, with an MIC of >10,000 μg/ml for the VRE test strain used in mouse models) promote colonization (7). Antibiotics that are active against anaerobes, that have relatively enhanced antienterococcal activity, and that are excreted in high concentrations in bile (e.g., piperacillin-tazobactam, with an MIC of 625 μg/ml for the VRE test strain) may inhibit the establishment of VRE colonization during treatment (7, 16). However, piperacillin-tazobactam may also promote the establishment of colonization when exposure to VRE occurs after treatment and prior to recovery of the anaerobic microflora (7, 16). In addition, once VRE colonization is established, piperacillin-tazobactam and ampicillin-sulbactam promote persistent overgrowth in mice and in colonized human patients (6, 7, 16).

Because expanded-spectrum cephalosporins have frequently been associated with colonization with VRE, formulary modifications that involve restrictions on the use of these agents have been suggested as control measures. However, the optimal agents that might be substituted for expanded-spectrum cephalosporins as a means of limiting colonization with VRE are unknown. Beta-lactam–beta-lactamase inhibitor combinations such as piperacillin-tazobactam have often been chosen as substitutes for expanded-spectrum cephalosporins because they have rarely been associated with VRE in clinical studies and because they inhibit the establishment of colonization in mice (2, 6, 7, 8, 9, 13–15). Such formulary substitutions have been associated with reductions in colonization with VRE in some but not all published studies (2, 8, 9, 11, 13, 14). As noted above, however, beta-lactam–beta-lactamase inhibitor combinations may promote colonization with VRE in some circumstances (7, 16). In addition, it has not been confirmed that agents such as piperacillin-tazobactam inhibit the establishment of colonization with VRE during treatment in humans. Agents that do not disrupt intestinal anaerobes (e.g., cefepime

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and aztreonam) offer another alternative to expanded-spectrum cephalosporins that alter anaerobic microflora; however, the potential advantage of these agents may not be realized in clinical settings, in which they are frequently administered in combination or in sequence with other agents that may promote colonization with VRE.

In this study, we compared the frequency of acquisition of rectal colonization with VRE among intensive care unit (ICU) patients receiving cefepime-containing antibiotic regimens versus those receiving piperacillin-tazobactam-containing antibiotic regimens. Other expanded-spectrum cephalosporins were not included as a comparison group because these agents are rarely used in the study units. Our goal was to evaluate the acquisition of VRE in a real-world setting in which the antibiotics of interest might often be given in sequence or in combination with other antimicrobials. We hypothesized that piperacillin-tazobactam-containing regimens might be associated with lower rates of acquisition of VRE in such settings because the inhibitory activity of piperacillin against VRE would be maintained, despite the disruption of the indigenous microflora by other agents. Because piperacillin-tazobactam inhibits the establishment of colonization with VRE during treatment in mice, we hypothesized that the acquisition of colonization with VRE would be particularly uncommon during the course of therapy with this agent. Finally, we also examined the frequency of persistence of colonization with VRE among patients with positive rectal swab cultures for VRE prior to the initiation of therapy.

MATERIALS AND METHODS

Setting and study design. The University of Pittsburgh Medical Center is an 800-bed tertiary-care referral center and a level 1 trauma center. VRE has been endemic in the medical center since the early 1990s. There are approximately 120 ICU beds spread among several ICUs. Consecutive patients in these ICUs who had commenced with treatment with either piperacillin-tazobactam or cefepime were assessed for the new detection of stool colonization with VRE as a quality assurance project of the hospital's antibiotic management program. In these ICUs, piperacillin-tazobactam and cefepime were the two most widely used beta-lactam antibiotics with antipseudomonal activities. Rectal swabs were obtained on a weekly basis from patients in each ICU and were cultured for VRE as part of routine infection control surveillance efforts.

The prior use of any antibiotic that was administered in the 30 days before the piperacillin-tazobactam or cefepime course was assessed. Patients who had received either piperacillin-tazobactam or cefepime in this 30-day period were excluded from further analysis. Prior therapy was defined as that which included antibiotics with activities against anaerobic organisms if it comprised therapy with metronidazole, clindamycin, ticarcillin-clavulanate, imipenem, meropenem, ertapenem, amoxicillin-clavulanate, or ampicillin-sulbactam (6).

The demographic details collected from all patients included age, gender, the length of hospital stay, the length of ICU stay before the patient received the course of piperacillin-tazobactam or cefepime, and the particular ICU in which the patient was accommodated. Infection types were defined as pneumonia, urinary tract infections, wound infections, intra-abdominal infections, and bloodstream infections, according to Centers for Disease Control and Prevention definitions. Information regarding the isolation of VRE from clinical cultures was obtained by a review of the Microbiology Laboratory records.

Patients were defined as acquiring rectal carriage of VRE if they were negative for VRE by analysis of rectal swabs before they received piperacillin-tazobactam- or cefepime-containing antibiotic regimens and if their rectal swabs became positive during the 30 days or in the 30 days after the initiation of this antibiotic therapy. For patients treated with piperacillin-tazobactam, we assessed whether the acquisition of VRE occurred during or after therapy because this agent inhibits the establishment of colonization during treatment in mice. For patients with positive cultures for VRE before they received piperacillin-tazobactam or cefepime, we assessed whether colonization persisted during and after the completion of treatment. Patients were excluded from the assessment of VRE acquisition or persistence only if they died or were discharged from the hospital.

Microbiologic analysis. In order to screen for VRE, rectal swabs were plated onto Enterococcosel agar containing vancomycin (6 μg/ml). Identification and susceptibility testing were performed in accordance with the guidelines of the Clinical and Laboratory Standards Institute (formerly NCCLS) (10). Isolates of *Enterococcus gallinarum* and *E. casseliflavus*, species that are intrinsically resistant to low concentrations of vancomycin, were not included. Additional identification of the *Enterococcus* species to distinguish *E. faecium* from *E. faecalis* or other species was not routinely performed by the Microbiology Laboratory.

Statistical analysis. Data were analyzed by using SPSS software, version 10.0 (SPSS). Bivariate analyses were performed to compare the baseline characteristics of the cefepime- and piperacillin-tazobactam-treated patients who were evaluated for the new detection of VRE rectal colonization. Continuous data were analyzed by Student's unpaired *t* tests. Categorical data were analyzed by the Pearson chi-square test or Fisher's exact test. On the basis of previous infection control data, we estimated that ~20% of the patients with negative initial cultures would acquire colonization with VRE during their ICU admission. A power calculation indicated that the inclusion of 70 patients per group would provide a 77% power to detect a clinically significant reduction in the rate of acquisition of VRE, which was defined as a reduction from 20% to 5%.

RESULTS

Patient characteristics. Four-hundred seventy patients commenced on piperacillin-tazobactam or cefepime were assessed (235 patients received piperacillin-tazobactam and 235 patients received cefepime). Of these, 29 patients who received piperacillin-tazobactam and 44 patients who received cefepime had received either piperacillin-tazobactam or cefepime in the 30 days prior to the initiation of the study antibiotic treatment in the ICU and so were excluded from further analysis. Of the remaining 397 patients, 52 (13%) were colonized with VRE before they began therapy with cefepime or piperacillin-tazobactam. Of these 397 patients, 146 were eligible for the analysis of VRE acquisition because they had a rectal swab negative for VRE before they commenced piperacillin-tazobactam (72 patients) or cefepime (74 patients) therapy and had a follow-up rectal swab analysis performed in the 30 days after antibiotic therapy commenced.

Table 1 shows a comparison of the baseline characteristics of the 146 cefepime- and piperacillin-tazobactam-treated patients who were evaluated for the acquisition of VRE. Cefepime-treated patients had significantly longer prior hospital and ICU stays and were more likely to have been cared for in the Cardiothoracic ICU and to have received therapy with the study antibiotics for pneumonia. Antibiotic therapy was administered frequently in the 30 days prior to the commencement of the piperacillin-tazobactam- and cefepime-containing regimens, and the patients in the cefepime group were significantly more likely to have received prior antibiotic therapy (59/74 [79.7%] and 35/72 [48.6%], respectively; $P < 0.001$).

VRE acquisition. Of the 146 patients assessed for the acquisition of VRE, 42 (28.8%) had the new detection of VRE rectal colonization. There were no significant differences in the acquisition of VRE between patients receiving piperacillin-tazobactam (19/72 patients; 26.4%) and those receiving cefepime (23/74 patients; 31.1%) ($P = 0.28$) (Table 2). Of the 19 patients who acquired VRE in association with piperacillin-tazobactam therapy, 10 (53%) developed the new detection of VRE during the course of piperacillin-tazobactam treatment. Of the 23 patients who acquired VRE in association with cefepime therapy, 11 (48%) developed the new detection of VRE during the course of cefepime therapy. The number of

TABLE 1. Comparison of baseline characteristics of 146 ICU patients treated with cefepime and those of patients treated with piperacillin-tazobactam-containing antibiotic regimens and evaluated for new detection of rectal colonization with VRE

Variable	Cefepime (n = 74)	Piperacillin-tazobactam (n = 72)	P
Male gender (no. [%])	43 (58.1)	37 (51.4)	0.20
Age (yr [mean ± SD])	58.9 ± 18.1	61.4 ± 17.5	0.87
Prior no. of days in hospital (mean + SD)	10.2 ± 9.1	5.4 ± 7.1	0.04
Prior no. of days in ICU (mean + SD)	8.0 ± 7.2	3.3 ± 4.5	0.001
Any antibiotic treatment in prior 30 days (no. [%] of patients)[a]	59 (79.7)	35 (48.6)	<0.001
Vancomycin	38 (51.4)	11 (15.3)	<0.001
Expanded-spectrum cephalosporin	4 (5.4)	3 (4.2)	0.73
Fluoroquinolone	30 (40.5)	14 (19.4)	0.005
Agent with activity against anaerobes	42 (56.8)	8 (11.1)	<0.001
Clindamycin	3 (4.1)	1 (1.4)	0.32
Infection type (no. [%] of patients)			
Pneumonia	31 (41.9)	15 (20.8)	0.008
Urinary tract infection	13 (17.6)	13 (18.1)	1.0
Bloodstream infection	13 (17.6)	7 (9.7)	0.23
ICU type (no. [%] of patients)			
Medical	19 (25.7)	27 (37.5)	0.20
Cardiothoracic	23 (31.1)	5 (6.9)	<0.001
Neonatal	6 (8.1)	6 (8.3)	0.76
Trauma	5 (6.8)	8 (11.1)	0.84
Coronary care	5 (6.8)	7 (9.7)	0.73
Surgical	4 (5.4)	4 (5.6)	0.98
Other	12 (16.2)	15 (20.8)	0.36

[a] Clindamycin was a subset of agents with activity against anaerobes. Vancomycin included only patients receiving intravenous therapy.

swabs collected to assess the acquisition of VRE did not differ between the piperacillin-tazobactam and the cefepime groups (2.3 ± 0.4 and 2.5 ± 0.7, respectively; $P = 0.52$).

Persistence of established VRE colonization. Eighteen additional patients were eligible for analysis of the effect of antibiotic therapy on the persistence of established colonization because they had a positive rectal swab culture for VRE before they commenced piperacillin-tazobactam (8 patients) or cefepime (10 patients) therapy and had a follow-up rectal swab performed in the 30 days after antibiotic therapy commenced. One hundred percent of the cefepime-treated patients continued to have positive cultures for VRE during or after the completion of the course of treatment, whereas 88% (seven of eight) of the piperacillin-tazobactam-treated patients continued to have positive cultures for VRE ($P > 0.20$).

TABLE 2. Comparison of rates of new detection of colonization and infection with VRE among 146 ICU patients treated with cefepime-containing antibiotic regimens and those among patients treated with piperacillin-tazobactam-containing antibiotic regimens

Parameter	No. (%) of patients treated with:		P
	Cefepime (n = 74)	Piperacillin-tazobactam (n = 72)	
VRE colonization	23 (31.1)	19 (26.4)	0.28
VRE infection	5 (6.8)	4 (5.6)	0.20

Isolation of VRE from clinical cultures. Of 397 patients who had not received therapy with piperacillin-tazobactam or cefepime in the 30 days prior to the initiation of therapy in the ICU, 25 (6.3%) had VRE isolated from cultures of clinical specimens. There was no significant difference in the frequency of isolation of VRE from clinical specimen cultures between patients treated with piperacillin-tazobactam (4.9%; 10 of 206) and those treated with cefepime (7.9%; 15 of 191) ($P = 0.20$).

DISCUSSION

Our findings do not provide support for our hypothesis that in ICU settings piperacillin-tazobactam-containing antibiotic regimens may be associated with lower rates of VRE acquisition than cefepime-containing regimens. There was a nonsignificant increase in the frequency of VRE acquisition in the cefepime group; however, patients receiving cefepime had significantly longer prior hospital and ICU stays and were more likely to have received antibiotics in the preceding 30 days. Cefepime-treated patients were more likely than piperacillin-tazobactam-treated patients to have been cared for in the Cardiothoracic ICU; however, it is unlikely that this biased the results in favor of cefepime because the frequency of VRE acquisition was high for both groups of patients in the unit (12 of 23 [52%] cefepime-treated patients and 2 of 5 [40%] piperacillin-tazobactam-treated patients on the unit acquired colonization with VRE). In fact, we reanalyzed the data after exclusion of the Cardiothoracic ICU patients and found that

11/51 (22%) cefepime-treated patients versus 17/67 (25%) piperacillin-tazobactam-treated patients acquired VRE colonization ($P = 0.23$). Of the patients with known VRE colonization prior to the beginning of therapy, the piperacillin-tazobactam- and the cefepime-containing regimens were associated with persistent positive stool cultures in 88% and 100% of patients, respectively. These findings demonstrate that both piperacillin-tazobactam therapy and cefepime therapy may be associated with the frequent acquisition and persistence of VRE in real-world ICU settings.

Although piperacillin-tazobactam may inhibit the establishment of colonization with VRE in mice when exposure occurs during treatment (7, 16), we are aware of only one previous study that prospectively examined the acquisition of rectal colonization with VRE during therapy with this agent in patients. DiNubile et al. (4) found that only 1.6% of piperacillin-tazobactam-treated patients with intra-abdominal infections acquired VRE during therapy, whereas 6.4% of ertapenem recipients with intra-abdominal infections acquired VRE during therapy. However, because end-of-therapy stool specimens could be collected up to 3 days after the discontinuation of therapy in that study, it is not possible to assess whether VRE was acquired during or shortly after the completion of therapy (4).

Of the 19 patients who acquired VRE in association with piperacillin-tazobactam therapy in our study, 10 (53%) developed the new detection of VRE during the course of therapy. One possible explanation for the discrepancy between our current findings and those of previous studies with mouse models is that some patients may have had low levels of VRE in the intestinal tract prior to the beginning of piperacillin-tazobactam therapy (i.e., the finding of new positive rectal swab cultures could represent the new detection of colonization due to the expansion of preexisting VRE populations rather than the exogenous acquisition of VRE). In fact, we have found that modification of the previous mouse model (16) to include orogastric inoculation of 10,000 CFU of VRE 1 day prior to the beginning of piperacillin-tazobactam therapy results in the reduced efficacy of the therapy in preventing the establishment of colonization (50% versus 0% colonization rates for controls receiving VRE concurrently with the initiation of piperacillin-tazobactam treatment) (the authors' unpublished data). Because rectal swab cultures may have poor sensitivity for the detection of low-density VRE colonization (lower limit of detection, ~4 $\log_{10}$ CFU/g of stool) (3), our current study may have not detected low levels of VRE present prior to the initiation of therapy. Also, it is plausible that patients may repeatedly ingest small numbers of VRE cells while receiving antibiotic regimens, whereas a single oral inoculum of VRE has typically been administered in studies with mouse models. The repeated ingestion of VRE during therapy could potentially increase the risk of acquiring colonization during piperacillin-tazobactam therapy in mice or in human patients (12). In addition, some clinical VRE isolates could be more resistant to inhibition by piperacillin-tazobactam than the VRE test strain used in the mouse model studies (piperacillin MIC, 625 μg/ml) (7), or relatively low concentrations of piperacillin could be excreted into the intestinal tracts of patients in comparison to the concentrations excreted into the intestinal tracts of mice. In fact, both Nord et al. (11) and Wilcox et al. (17) have demonstrated significant interpatient variability in the levels of piperacillin and tazobactam detected in the stools of patients. Finally, the concurrent use of other antibiotics in combination with piperacillin-tazobactam may have reduced the protective effect of this agent in patients.

Although our current and previous findings (6) suggest that piperacillin-tazobactam therapy may promote VRE colonization in patients, this agent has not been associated with VRE in case-control studies. However, it is notable that many clinical studies either have failed to look for an association between piperacillin-tazobactam and VRE or have grouped penicillins together for the purposes of analysis. For example, of 14 such studies included in a review of antimicrobial risk factors for colonization with VRE, 5 (36%) included "penicillins" in the analysis and 9 (65%) either definitely did not include penicillins in the analysis or provided insufficient details to determine whether penicillins were included (5). The grouping of penicillins together is problematic, because these agents differ significantly in their biliary excretion and in their activities against enterococci and anaerobic organisms. In addition, many studies that evaluated antimicrobial risk factors for colonization with VRE were conducted prior to the emergence of piperacillin-tazobactam as a "workhorse" antibiotic in the United States.

Cefepime is excreted in minimal concentrations into bile and does not cause a significant disruption of the anaerobic microflora in the stools of healthy humans (1). Because most cefepime-treated patients who developed the new detection of colonization with VRE had received therapy with other antibiotics in the prior 30 days, it is not possible to determine if colonization with VRE was promoted by cefepime or by the other antibiotics. In theory, choosing antibiotics that have a relatively little effect on the anaerobic microflora of the colon could be a useful strategy for limiting the spread of VRE (6, 7). Additional studies are needed to examine the effect of cefepime (and of other agents that cause a minimal disruption of the anaerobic microflora) on colonization with VRE in settings in which this agent is used as monotherapy in patients who have not recently received antibiotic therapy.

Our study has several limitations. First, we did not precisely measure the level of adherence to the culture protocol, and we did not perform a time-dependent analysis of the rate and timing of VRE acquisition. However, the overall rate of compliance with weekly rectal swab surveillance cultures in the ICUs during the year of the study was greater than 80% (authors' unpublished data), and the number of swabs collected to assess the acquisition of VRE did not differ between the two groups. Second, because the treatment groups were not randomized, it is possible that there were differences among the groups, in addition to those discussed above, that might have affected the risk of acquiring VRE. Finally, the species of the VRE isolates from the study patients were not determined and the isolates were not subjected to molecular typing, so we cannot exclude the possibility that clonal outbreaks were occurring in some of the ICUs. However, a hospital-wide culture survey in 2000 demonstrated that 95% of the VRE isolates were *E. faecium* and six distinct clones were identified by pulsed-field gel electrophoresis (PFGE). On the basis of the infection control records, no significant increases in the rates of VRE colonization or infection were noted in the ICUs during the

study period. In addition, PFGE of 18 VRE isolates from the Cardiothoracic ICU at the time of the study demonstrated the presence of five distinct PFGE clones.

In summary, the rate of new detection of VRE rectal colonization did not differ significantly among ICU patients receiving piperacillin-tazobactam versus those receiving cefepime-containing antibiotic regimens. The new detection of VRE in association with piperacillin-tazobactam therapy frequently occurred during the course of therapy, suggesting that this agent may not inhibit the exogenous acquisition of VRE in patients. However, additional studies by the use of broth enrichment cultures or PCR are needed to exclude the possibility that piperacillin-tazobactam therapy caused the expansion of preexisting VRE populations that were not detected by using rectal swabs. Although formulary substitutions of piperacillin-tazobactam or cefepime for expanded-spectrum cephalosporins offer a potential strategy for controlling colonization with VRE, our data suggest that neither of these agents is likely to provide a panacea for the control of this important nosocomial pathogen.

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